

Clinical Trial Protocol

TITLE: Prospective, Multicenter, Randomized, Single-blind, Parallel-controlled Clinical Trial Protocol for the Safety and Efficacy of Clinical Applications of the Endoscopic Instrument Control System

PROTOCOL ID: SDWG-NST600S-CT

DOCUMENT TYPE: Statistical analysis plan

DATE: 2019-09-01

SPONSOR: The Third Xiangya Hospital of Central South University

COLLABORATOR: The Affiliated Hospital of Qingdao University

Statistical analysis plan

1. Statistical design, methods, and analysis regulation

1.1 General principles of statistical analysis

This study uses SAS 9.4 for data description and analysis.

All statistical tests are performed by one-sided test, with the significant level, α , set at 0.025. The confidence interval adopted bilateral 95% confidence level.

Quantitative indicators are described by mean, standard deviation, P25, P75, minimum and maximum.

Categorical and ordinal categorical indicators are described in case number and percentage of each category.

Group t-test (normal distribution) or Wilcoxon rank sum test are used to conduct group comparisons of quantitative indicators according to the data distribution. Categorical indications are compared through the Pearson χ^2 test or the Fisher's exact test. The Wilcoxon rank sum test is used for ordinal categorical indicators.

According to the research data, it is necessary to judge whether there is a central effect and consider whether there is an interaction effect between the central effect and the intervention when the indicators have the central effect. Indexes with central effect need to be corrected before statistical analysis and comparison.

1.2 Completion status and baseline analysis

Summarize the patient enrollment and population division of the center.

Describe the basic demographic characteristics and related indicators of effectiveness statistically when the cases are enrolled.

1.3 Validity evaluation

1.3.1 Primary outcome measures

Non-inferiority test is used for the primary outcome measures of the surgical success

rate, and the testing hypothesis is as follows:

$$H_0 = \pi_{\text{experimental group}} - \pi_{\text{control group}} \leq -10\%$$

$$H_1 = \pi_{\text{experimental group}} - \pi_{\text{control group}} > 10\%$$

The Pearson χ^2 test or the Fisher's exact test is performed on the surgical success rate between the experimental group and the control group, and a 95% confidence interval is calculated for the difference value of the surgical success rate between the two groups.

1.3.2 Secondary outcome measures

During the evaluation and analysis of Endoscopic Instrument Manipulate System, the independent sample t-test or Wilcoxon rank sum test is used for quantitative indicators, and the Pearson χ^2 test is used for qualitative indicators.

1.4 Safety analysis

1.4.1 Safety parameter analysis

Describe the measured results of vital signs, laboratory examination, physical examination and other safety indicators when normal before treatment and abnormal after treatment, and list the number and proportion of cases. Adverse events are described by the number and incidence of adverse events, and the proportion of subjects with adverse events is compared between groups by Pearson χ^2 test or the Fisher's exact test. At the same time, all of the adverse events in each group are described in detail, including their manifestations, degrees and their relationship with the study instruments.

1.4.2 Safety evaluation

The incidence of operation-related organ and vascular injury is compared between the experimental group and the control group.

2. The specific implementation method of single-blindness

2.1 Reasons for choosing single-blindness

In order to strictly guarantee the homogeneity and uniformity of the researcher, the operator is required to have certain qualifications that the operator must have at least one

year of experience in robotic surgery, and have been professionally trained and obtained the certificate of test product operation training. When the surgeon is performing a surgical operation, it is inevitable to find out the type of device being used. Therefore, complete double blindness cannot be achieved, and single blindness is selected.

2.2 The implementation method of single-blindness

2.2.1 Blinding code generation and numbering grouping

According to the protocol approved by the sponsor, the statistician used the SAS software to randomize and create random tables for the trial to generate blinding code, which is confirmed by the third party designer. Personnel of the first group who has nothing to do with the study groups the subjects enrolled according to the blinding code. After the second group of research-independent personnel checks the group information and then the group information is sealed in an envelope and saved by a third party researcher who does not participate in the operation. All the enrolled subjects are enrolled into the experimental group or the control group for treatment according to the random number.

2.2.2 Blinding maintenance

(1) The subjects

Subjects are not aware of the enrollment information before, during, and after surgery, and the research personnel are strictly confidential on group information. During the operation, the masking technique is adopted for the test product and the control product, and the product is shielded by the curtain to prevent the subject from knowing the product type.

(2) Safekeeping of random envelopes

The envelope information should be kept strictly confidential before the operation. Only when the subject is to be scheduled for surgery can the envelope be removed to inform the investigator of the enrollment information. Keep envelope information strictly confidential to avoid blinding code disclosure.

3. Measures to reduce and avoid bias

The following measures are planned during the trial to reduce or avoid bias:

(1) SAS software is used for randomization and generating the random table. According to the order of the random numbers, the enrolled subjects are grouped by a third party or a researcher who is not involved in the study. The grouping information is sealed in an envelope and stored by third parties or researchers who are not involved in the study. All the enrolled subjects are treated according to a random number in the experimental group or the control group to avoid bias caused by sampling without random selection of cases.

(2) The sample size required for the experiment is calculated statistically and met the statistical requirements to avoid bias caused by the small sample size.

(3) Before the start of the experiment, the researchers participating in the study should be uniformly trained and tested strictly in accordance with the protocol, so as to avoid the bias caused by the researchers violating the protocol during the study.

(4) The clinical trial protocol established a uniform recording method and judgment standard to avoid the bias caused by the subjective tendency of the researcher.

(5) During the course of this study, clinical supervisors appointed by the sponsor will make regular on-site visits to the research hospital to ensure that all contents of the research program are strictly observed and the research materials are correctly filled in in order to avoid the bias caused by the non-standard test operation and research data filling.

(6) After the end of the experiment, EpiData 3.0 software is used for entry and verification of the experimental data. It is up to the researcher to confirm all data doubts and data quality to avoid bias caused by data entry errors.

4. Calculation of sample size

4.1 The total sample size

168 subjects are expected to be enrolled.

4.2 The subject number of clinical trials and the reasons for its determination

According to the literature and clinical expert consensus, the control equipment surgical

success rate is no less than 95% (reference: Zeus robot-assisted laparoscopic cholecystectomy in comparison with conventional laparoscopic cholecystectomy). The non-inferiority design of positive control is adopted in this study, and the sample size calculation formula is as follows:

$$n_c = \frac{(z_{1-\beta} + z_{1-\alpha})^2}{(\Delta - \delta)^2} [\pi_c * (1 - \pi_c) + \frac{\pi_r * (1 - \pi_r)}{r}]$$

Take $\alpha = 0.025$ (one-sided), $\beta = 0.2$ (power of test: 80%), and non-inferiority margin $\Delta = 10\%$. Cases in the experimental group and the control group are equally proportioned. Considering that the drop-out rate of subject is about 10% during the experiment, this study plans to enroll 84 cases in the experimental group and 84 cases in the control group, a total of 168 cases.

4.3 Number of subjects per clinical trial institution

There are 84 cases in the planned experimental group and 84 cases in the control group, 168 cases in total. Two hospitals share equally.

5. Significance level and power of clinical trials

Set $\alpha = 0.025$, $1 - \beta = 0.8$.

6. Expected rate of drop-out

The expected rate of drop-out does not exceed 10%.

7. Qualification/disqualification criteria for clinical trial results

The evaluation criteria of whether the test results are qualified or not are considered from two aspects: The first is the standardization of the clinical trial, that is, whether the trial is completed according to the requirements of the program. The second is the fairness of result evaluation.

According to the non-inferiority test, when the lower limit of 95% CI of the difference value between the two groups' surgical success rate is greater than -10%, it can be

considered as meeting the qualified requirements of the test in this study.

8. Statistical methods of all data, together with missing, unused or incorrect data (including exiting and withdrawal during the study) and processing methods of unreasonable data

After the database is locked, statistical analysis programming and logic detection programming are performed according to the statistical analysis plan. A statistical analysis report is issued based on the results.

The processing of outlier data is based on the questioning and determination of the unreasonable data of the researcher in the form of an answer sheet written by the data manager.

9. Reporting procedures of deviation from the original statistical plan

In the case of "incomplete implementation of the statistical analysis plan", the change of procedure should be applied in advance. For example, the change of the statistical analysis plan should be truthfully recorded in the statistical analysis plan, including the place, reason and time of change and other revision records.

10. Selection criteria and rationale for subjects included in the analysis

Full analysis set (FAS): A set of subjects according to the Intention To Treat (ITT) principle referring to a data set consisting of all subjects who participated in the treatment and had a baseline efficacy evaluation.

Per Protocol Set (PPS): The treatment groups that completed the trial and excluded the situation of severe violation scheme (referring to the subjects' violation of the inclusion criteria or exclusion criteria), and whose data on major indicators are available.

Safety Analysis Set (SAS): A collection of subjects who are randomly grouped, used the device under test, and had at least one baseline layer safety assessment.

The effectiveness analysis will be based on the Full Analysis Set and the Per Protocol

Set. All baseline demographic analysis will be based on a full analysis set and safety evaluation will be performed on the Safety Analysis Set.